

Review Article

The role of folate in malaria – implications for home fortification programmes among children aged 6–59 months

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Folic acid and iron supplementation has historically been recommended as the preferred anaemia control strategy among preschoolers in sub-Saharan Africa and other resource-poor settings, but home fortification of complementary foods with multiple micronutrient powders (MNPs) can now be considered the preferred approach. The World Health Organization endorses home fortification with MNPs containing at least iron, vitamin A and zinc to control childhood anaemia, and calls for concomitant malaria control strategies in malaria endemic regions. Among other micronutrients, current MNP formulations generally include 88 µg folic acid (corresponding to 100% of the Recommended Nutrient Intake). The risks and benefits of providing supplemental folic acid at these levels are unclear. The limited data available indicate that folate deficiency may not be a major public health problem among children living in sub-Saharan Africa and supplemental folic acid may therefore not have any benefits. Furthermore, supraphysiological, and possibly even physiological, folic acid dosages may favour *Plasmodium falciparum* growth, inhibit parasite clearance of sulphadoxine-pyrimethamine (SP)-treated malaria and increase subsequent recrudescence. Even though programmatic options to limit prophylactic SP use or to promote the use of insecticide treated bed nets may render the use of folic acid safer, programmatic barriers to these approaches are likely to persist. Research is needed to characterise the prevalence of folate deficiency among young children worldwide and to design safe MNP and other types of fortification approaches in sub-Saharan Africa. In parallel, updated global guidance is needed for MNP programmes in these regions.

Keywords: complementary foods, dietary recommendation, evidence-based practice, folate, micronutrients, nutrition-infection interaction.

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Background

Micronutrients regulate key physiological functions in the body and their deficiencies are a major public health problem worldwide (Black *et al.* 2008). Folate serves in single-carbon transfers in the synthesis of DNA and RNA and the metabolism of amino acids. Key folate-dependent reactions are the conversion of homocysteine to methionine for methylation

reactions and the conversion of deoxyuridylate to thymidylate to ensure proper cell division. Folate deficiency leads to a decline in serum folate and a rise in homocysteine levels, and impairs the reproduction of erythrocytes as evidenced by megaloblastic anaemia. Folate and vitamin B₁₂ metabolism is inter-related and may explain why deficiencies in either vitamin lead to megaloblastic anaemia (Kupka *et al.* 2008). The risk of neural tube defects is increased by

maternal periconceptual folate deficiency, but can be reduced by folic acid supplementation (Czeizel *et al.* 2011). Among children, folate deficiency is related to impaired cognitive development (Black 2008) and increased diarrhoeal and respiratory disease (Manger *et al.* 2011, Strand *et al.* 2007); however, folic acid supplementation shows little promise in reducing diarrheal and respiratory disease (Taneja *et al.* 2013).

Based on folate's role in erythropoiesis, folic acid is often given alongside iron in anaemia control programmes. Routine supplemental folic acid and iron has historically been recommended as an anaemia control strategy among children aged 6–23 months in settings where anaemia is common among this age group (WHO 2001). In 2006, a large trial conducted in an area with high rates of malaria transmission in Tanzania showed that the World Health Organization (WHO)-recommended routine folic acid and iron anaemia control strategy resulted in an overall increased risk of adverse events while showing benefits among iron deficient children (Sazawal *et al.* 2006). In response, a WHO/United Nations Children's Fund (UNICEF) joint statement called for the targeting of iron and folic acid supplementation to those who are anaemic and at risk of iron deficiency (WHO & UNICEF 2006). In 2007, a WHO consultation recommended that '[u]niversal iron supplementation (i.e. use of medicinal iron as pills or syrups) should not be implemented without the screening of individuals for iron deficiency . . .' (WHO 2007). With regard to folic acid, the consultation concluded that '[b]ecause widespread folate deficiency is not known

to be a problem in infants and young children, and supplemental folic acid may interfere with the efficacy of antifolate antimalarial drug therapy, supplemental folic acid or foods fortified with folic acid should not be given to infants and young children in areas where antifolate drugs are used', and that '[p]rocessed complementary foods fortified with folic acid should be avoided in order to avoid the potential interference of folic acid with antifolate antimalarial medications'.

At the time this guidance was issued, the realisation was growing that interventions were needed to improve the micronutrient content and overall nutritional quality of complementary foods as a key programmatic area, i.e. interventions that go beyond merely providing iron and folic acid supplementation. Commercially fortified foods could potentially address this concern but are not accessible to large parts of the population in poor countries. As a result, home fortification, either through small-quantity lipid-based nutritional supplements (LNS) or multiple micronutrient powders (MNPs), was considered as a promising approach to improve the nutritional quality of complementary foods. While LNS show promise in improving growth, motor development (Adu-Afarwuah *et al.* 2007), as well as iron and haemoglobin levels (Adu-Afarwuah *et al.* 2008), their programmatic use remains limited. Home fortification MNPs is supported by numerous studies and programmatic experiences indicating their effectiveness, acceptability and high benefit/cost ratio, and at least 22 countries around the world are currently implementing MNP interventions (Zlotkin *et al.* 2005; UNICEF & CDC 2013). However, the aforemen-

Key messages

- Home fortification with multiple micronutrient powders (MNPs) is an effective anaemia control strategy among preschool age children in sub-Saharan Africa and other regions with high anaemia prevalence.
- High dosages of supplemental folic acid should not be given to preschool age children in malaria-endemic areas as these supplements may favour growth of *Plasmodium falciparum*, inhibit parasite clearance of sulphadoxine-pyrimethamine-treated malaria and increase subsequent recrudescence.
- The benefits and safety of providing folic acid at levels of the Recommended Nutrient Intake through MNPs in malaria endemic regions is currently unclear.
- Research is needed to characterise the prevalence of folate deficiency among preschoolers in malaria-endemic regions and to test the safety and benefits of low-dose folic acid in MNPs using placebo-controlled, randomised trial designs.
- Updated global guidance is needed to inform current MNP programmes.

tioned WHO consultation also commented that 'iron preparations administered through home fortification, such as powders, crushable tablets, and fat-based products, should not be used in malaria-endemic areas (WHO 2007)'. As a result, the planning for MNP home fortification programmes came to a halt in malaria-endemic areas after this guidance was issued.

In 2011, WHO commissioned a Cochrane Review (De-Regil *et al.* 2011) of eight trials on MNPs (containing at a minimum vitamins A and C, folic acid, iron and zinc), including five trials in malaria-endemic areas. Based on the findings of the review, WHO in the same year provided new guidance on home fortification by recommending the use of home fortification with MNPs (containing at least iron, vitamin A and zinc) to improve iron status and reduce anaemia among infants and children 6–23 months of age (WHO 2011a). Even though the report indicated that the treatment effect on iron status and anaemia was not modified by malaria endemicity, it was not able to report on the incidence of malaria or other morbidities (De-Regil *et al.* 2011). The report nevertheless remarked, that in 'malaria-endemic areas, the provision of iron should be implemented in conjunction with measures to prevent, diagnose and treat malaria'. Since then, a placebo-controlled trial from a non-malarious region in Pakistan reconfirmed the benefits of providing daily Recommended Nutrient Intake (RNI) levels of iron, folic acid alongside other micronutrients on iron deficiency anaemia among children aged 6–24 months, but unexpectedly showed increases in diarrhoeal and respiratory morbidity (Soofi *et al.* 2013).

While this new WHO guidance makes it clear that home fortification with iron-containing products can proceed in the context of comprehensive malaria control, there is currently no updated guidance on whether, or at what quantities, folic acid in micronutrient powder programmes in malaria-endemic areas should be used. Even though the determination of the safe amounts of folic acid in areas with high malaria endemicity was identified as a research priority in the WHO guideline (WHO 2011a), there has been no concerted international effort to determine the safety and benefits of folic acid in MNPs.

In the absence of updated WHO guidance, a multiagency technical advisory group has developed recommendations on the nutrition composition of MNPs (Home Fortification Technical Advisory Group 2012). These state that one sachet of MNPs should contain 150 µg of Dietary Folate Equivalents (DFE) (88 µg folic acid). One sachet per day would thus cover 100% of the RNI of children aged 1–3 years and 188% of the RNI for children aged <12 months. Folic acid is also used in flour fortification programmes in sub-Saharan Africa and other settings. These programmes may make substantial contributions to the folate RNI if current specifications are followed (Dary 2008; WHO *et al.* 2009; Engle-Stone *et al.* 2012). On the other hand, weekly iron and folic supplementation programmes (recommended to provide weekly 25 mg iron and 300 µg folic acid to children aged 24–59 months) remain uncommon in sub-Saharan Africa (WHO 2011b).

Given the global support for MNP programmes among children, this paper reviews folate status and nutritional requirements among children aged 6–59 months, and examines the role of folate status and folic acid supplementation among children with regard to malaria. The review focuses on sub-Saharan Africa and infections caused by *Plasmodium falciparum*, which is the most common malaria parasite in this geographic region (Culleton *et al.* 2008). The review does not consider evidence from children with acute malnutrition, as they require specially formulated foods to treat their condition (Golden 2009) as well as adolescents, pregnant women and adults, unless the research was relevant for the general population of pre-school age children.

Prevalence estimates of folate deficiency among children

Efforts to estimate the prevalence of folate deficiency among children of pre-school age have been hampered by differences in cut-off levels used to determine deficient levels for the preferred indicators serum folate (considered to reflect recent folate intakes) and red blood cell folate (reflecting long-term folate status). Using plasma homocysteine concentrations as a functional indicator, a 2008 WHO

Technical Consultation recommended that folate deficiency should be defined in all age groups by concentrations $<10 \text{ nmol L}^{-1}$ (4 ng mL^{-1}) for serum folate and $<340 \text{ nmol L}^{-1}$ (151 ng mL^{-1}) for red blood cell folate (Selhub *et al.* 2008). The review noted, however, that higher levels may be needed during pregnancy to prevent neural tube defects.

A 2008 global review of folate status concluded that there was little nationally representative data available, and none from Africa or Asia. Of the available data, folate deficiency did not appear to be related to geographical distribution, the level of development or population groups (McLean *et al.* 2008). Subnational survey data from Africa collected before the onset of folic acid fortification programmes indicate that among school age children from Kenya (Siekman *et al.* 2003) and Nigeria (VanderJagt *et al.* 2000), the prevalence of plasma or serum folate deficiency (defined as $<6.8 \text{ nmol L}^{-1}$) was 0% and 2.4%, respectively. Other data from African children indicate that except for a study among Gambian preschoolers, among whom the prevalence of low red blood cell folate [defined as $<227 \text{ nmol L}^{-1}$ ($<100 \text{ ng mL}^{-1}$)] was approximately 24% and 18% in subsequent annual surveys (Fuller *et al.* 1988), folate deficiency appears to be uncommon. For instance, folate deficiency (defined as serum folate $<6.8 \text{ nmol L}^{-1}$) was absent among Malawian preschoolers with and without

severe anaemia (Calis *et al.* 2008). Furthermore, a recent national survey from Cameroon documented that merely 8.5% of children aged 12–59 months had plasma folate levels $<10 \text{ nmol L}^{-1}$ (Engle-Stone *et al.* 2012). These surveys did not measure homocysteine as a functional indicator of folate status or determined heterogeneity in folate metabolism related to the activity of 5,10-methylenetetrahydrofolate reductase (Molloy *et al.* 1997). Therefore, while available data from sub-Saharan Africa indicate that folate deficiency may not be common among preschoolers, the data is insufficient to adequately gauge the risk of folate deficiency in this geographic region.

Nutritional folate requirements

In an effort to determine nutritional folate requirements for all population age groups, the Food and Nutrition Board of the Institute of Medicine (IOM) determined the estimated adult average requirements and related estimates of the recommended dietary allowances (RDA) by analysing the required quantities of folate consumed under controlled conditions to maintain normal blood concentrations of erythrocyte folate, plasma homocysteine, and plasma or serum folate (Institute of Medicine 1998) (Table 1). In the absence of specific data to establish infant requirements for folate, an Adequate Intake for

Table 1. Recommended folate intakes expressed as dietary folate equivalents for preschool age children (Food and Nutrition Board and Institute of Medicine, 1998, World Health Organization and Food and Agricultural Organization. Vitamin and mineral requirements in human nutrition. 2nd ed. Geneva)*

Age group	Food and Nutrition Board, Institute of Medicine			FAO/WHO
	Estimated average requirement ($\mu\text{g d}^{-1}$)	Recommended dietary allowance ($\mu\text{g d}^{-1}$)	Tolerable upper level ($\mu\text{g d}^{-1}$) of folic acid from fortified foods or supplements	Recommended nutrient intake ($\mu\text{g d}^{-1}$)
0–6 months	65 [†]	— [‡]	— [§]	80
7–12 months	80 [†]	— [‡]	— [§]	80
1–3 years	120	150	300	150
4–8 years	160	200	400	200 [¶]

*1 dietary folate equivalent = $1 \mu\text{g}$ food folate = $0.6 \mu\text{g}$ folic acid from fortified food or folic acid from a supplement consumed with food = $0.5 \mu\text{g}$ of folic acid from a supplement consumed on an empty stomach.

[†]Adequate intake.

[‡]In the absence of an estimated average requirement, no RDA could be specified for this group.

[§]Not possible to establish.

[¶]Expressed for children aged 4–6 years.

infants aged 0–6 months was determined based on average breast milk folate concentrations and breast milk intakes, and for infants aged 7–12 months using extrapolations from adult requirements. The IOM report states that there is no health risk and thus no IOM tolerable upper level (UL) for folate consumed from natural sources. However, there is an UL for synthetic folate (folic acid) consumed from fortified foods and/or supplements for children and adults, but due to a lack of data not for infants. The adult UL was based on the potential of excessive folic acid intake to precipitate or exacerbate neuropathy in vitamin B₁₂-deficient adults, while the UL for children aged ≥1 years was derived by extrapolation from the adult UL (Institute of Medicine 1998).

Food and Agriculture Organization (FAO)/WHO subsequently adopted the IOM RDA estimates as the basis for the RNI. These RNI values indicate that children aged <12 months require 80 µg DFE per day, while the requirements increase to 150 and 200 µg DFE for the age groups 1–3 and 4–8 years, respectively.

Taking into account average breast milk intakes, breastfeeding children should take in daily amounts (in µg DFE) of 23, 28 and 103 at ages 6–8, 9–11 and 12–24 months, respectively, through complementary foods (Allen 2003). There is little data on folate intake among young children, but folate is generally not considered a problem nutrient during the complementary feeding period (Gibson *et al.* 1998).

Folate and malaria

The aforementioned recommendations developed by the IOM and FAO/WHO were developed for healthy populations. For children with anaemia caused by *P. falciparum*, it has been suggested that the erythroid hyperplasia observed after recurrent malarial haemolysis can deplete folate stores, increase folate requirements, and lead to megaloblastic anaemia (Menendez *et al.* 2000). As a result, mega dosages of folic acid have been used among children recovering from *P. falciparum*-related anaemia, but the potential harms and benefits of this practice for *P. falciparum* parasitaemia remain unclear (Mulenga *et al.* 2006).

Folate is not only required for the host but also for the malaria parasite. As a result, the parasite's folate metabolism has been an important target for antimalarial medications that are folate antagonists. Historically, the most common of these drugs used in Africa against *P. falciparum* is sulphadoxine-pyrimethamine (SP; Fansidar). Other antifolate drugs include pyrimethamine-sulfalene (Metakelfin), atovaquone-proguanil (Malarone; primarily used among those travelling to Africa), chlorproguanil-dapsone (Lapdap; withdrawn from markets in 2008), and pyrimethamine dapsone (Maloprim; recommended as a second-line drug only because of bone marrow side effects). The molecular target of these antifolate drugs are the enzymes dihydrofolate reductase and dihydropteroate synthase, which are required in folate metabolic pathways (Hyde 2005; Metz 2007). Owing to their antifolate action, drugs such as SP should only be used with caution among those who are already folate deficient (RxMed Pharmaceutical Information-Fansidar; [http://www.rxmed.com/b.main/b2.pharmaceutical/b2.1.monographs/CPS-%20Monographs/CPS-%20\(General%20Monographs-%20F\)/FANSIDAR.html](http://www.rxmed.com/b.main/b2.pharmaceutical/b2.1.monographs/CPS-%20Monographs/CPS-%20(General%20Monographs-%20F)/FANSIDAR.html)).

The documentation of *P. falciparum* resistance to antifolate antimalarial drugs called for an introduction of artemisinin-based combination therapy (ACT) as the recommended first-line malaria treatment, especially for *P. falciparum* malaria (WHO 2011c). Despite the current recommendations to use ACT as first-line antimalarial treatment, SP remains in use throughout sub-Saharan Africa to treat malaria among children and adults. In nationally representative surveys conducted in six sub-Saharan countries from 2009 to 2010 where ACT is recommended for the first-line malaria treatment, ACT availability and market share through private-sector outlets (where most anti-malarials are accessed) were generally low (O'Connell *et al.* 2011). On the other hand, SP remained widely available and made up the largest market share of non-artemisinin therapies. Even though this may partly be due to the fact that SP is recommended for the intermittent preventive treatment (IPT) in pregnancy in these countries, it is likely that SP is also commonly used for the treatment of clinical malaria among all age groups. This is

supported by the fact that in the private sector ACT is 10–20 times more expensive than SP (Amin & Snow 2005; Larson *et al.* 2006) and that provider knowledge on ACT as the first-line treatment is generally low, especially in the private sector (Larson *et al.* 2006; Wafula & Goodman 2010)

SP is also likely to remain in use because WHO has recommended since 2009 its use for the intermittent preventive treatment of malaria among infants (IPTi) (WHO 2010). This strategy should be implemented in areas with moderate to high malaria transmission and where parasite resistance to SP is not high. At defined intervals (generally 10 weeks, 14 weeks and ~9 months of age) corresponding to the routine schedule of the Expanded Programme on Immunization, children should receive a full therapeutic course of SP. IPTi implementation remains low; in fact, as of 2011, no country globally had adopted IPT among infants as national policy. For the Sahel subregion in Africa, WHO has recommended since 2013 the Seasonal Malaria Chemoprevention (SMC) instead of IPTi (WHO 2012). SMC consists of a complete treatment course of amodiaquine plus SP among children aged between 3 and 59 months at monthly intervals, beginning at the start of the transmission season, to a maximum of four doses during the malaria transmission season.

Interaction between folate status and antifolate antimalarial drugs

Antifolate antimalarial drugs attempt to inhibit the malaria parasite's folate metabolism. As a result, there is concern that high host folate status may favour growth of *P. falciparum* (Oppenheimer & Cashin 1986) and impair the effectiveness of antifolate drugs, especially given that some parasite strains can access exogenous folate and thus bypass drug-impaired folate synthesis (Macreadie *et al.* 2000). In animal studies, severe folate deficiency among rhesus monkeys protected against clinical disease and replication of the malaria parasite (Das *et al.* 1992), whereas folate deficiency in chickens increased the severity of malarial infection (Seeler & Ott 1945). Several *in vitro* studies demonstrated that addition of folic acid to the test media inhibited the

action of antifolate drugs. In a study by Watkins *et al.* (1985), folic acid concentrations above 40 nmol L⁻¹ markedly inhibited the action of sulphadoxine against *P. falciparum*, while Chulay *et al.* (1984) observed an inhibition at levels of 23 nmol L⁻¹. Salcedo-Sora *et al.* (2011) and Kinyanjui *et al.* (1999) used higher folic acid concentrations in *P. falciparum* and found inhibitory effects of folic acid for sulphadoxine and pyrimethamine, respectively. Given that physiological levels of folic acid inhibited antifolate antimalarial drugs, these findings may indicate that a similar drug inhibition may occur even at apparently normal or after low-dose folic acid supplementation in humans. Evidence from human studies is presented in subsequent sections.

Observational human studies

Among humans, the evidence from observational studies on folate status and malarial morbidity is mixed (Metz 2007). Megaloblastic anaemia, a sign of folate and/or B₁₂ deficiency, was related to greater malarial infection rates in an observational study among children from Nigeria (Fleming & Werblinska 1982), in line with the hypothesis that folate deficiency may increase susceptibility to malaria (Brabin 1982). The absence of folate deficiency and megaloblastic anaemia was hypothesised to be of relevance for low malaria infection rates observed among pregnant women from Uganda, but other explanations could not be ruled out (Hamilton *et al.* 1972). In a study among Sudanese children with *P. falciparum* malaria, homocysteine levels were significantly higher in children with recurrent and slide-confirmed malaria compared to healthy controls (Abdel *et al.* 2009). This observation indicates that deficiencies in vitamins B₆, B₁₂ or folate may increase risk of malaria infection, but the study was unable to establish whether the deficiencies are the result or the cause of malaria infection.

In contrast, there was no relation between blood folate levels and *P. falciparum* infection status in a study among adults and children in Benin (Hercberg *et al.* 1986). Among children suffering from malaria, several studies from sub-Saharan Africa indicate that red blood cell folate levels are either normal or

higher than among age-matched controls without malaria (Brabin 1985; Bradley-Moore *et al.* 1985; Oppenheimer & Cashin 1986; Abdalla 1990; van Hensbroek *et al.* 1995; Dzinjalama *et al.* 2005; Mulenga *et al.* 2006; Metz 2007).

However, observational studies on the relation between high host folate status malaria susceptibility are difficult to interpret (Metz 2007; Shankar 2008). Elevated folate levels may be due to *de novo* parasite folate synthesis (Trager 1959; Reid & Friedkin 1973), altered folate utilisation in infected red blood cells (Siddiqui & Trager 1964) or reticulocytosis (Brabin *et al.* 1986). Therefore, a PubMed search was performed using the search terms 'malaria', 'folic acid' and 'children' to identify prophylactic and therapeutic trials with an intervention group in which folic acid was provided (possibly alongside other micronutrients) and a comparison group without folic acid.

Prophylactic trials

In prophylactic trials among children, folic acid was provided alongside other micronutrients and children were followed for the development of malaria and other endpoints. In the aforementioned trial from Pemba, Tanzania, routine daily supplemental iron and folic acid (12.5 mg iron and 50 µg folic acid; half the dose for children aged 1–11 months) increased the risk of severe illness or death among pre-school children (Table 2). However, a substudy with more intensive malaria diagnosis and management (using SP) did not show such adverse effects related to severe illness or death, recovery from SP-treated malaria episodes or subsequent recrudescence (Sazawal *et al.* 2006). Among iron deficient children in the substudy, the trial regimen furthermore reduced malaria-related death or hospital admission [Relative Risk = 0.56 (0.32–0.97)]. Another placebo-controlled trial from Tanzania examined the effects of daily supplements of 18 mg iron and 93.75 µg folic acid alongside six other micronutrients, with or without zinc, on malaria incidence among children aged 6–60 months. Compared to placebo, multiple micronutrients decreased the time to first malaria episode but had no effect on overall malaria incidence. However, multi-

ple micronutrients appeared to increase malaria incidence in the subgroup of children with iron deficiency at baseline, but not in the subgroup without iron deficiency (Veenemans *et al.* 2011). In a third trial from Tanzania, conducted among HIV-exposed children aged 6 weeks, 130 µg folic acid (increased to 260 µg starting at age 6 months) alongside seven other vitamins did not have an effect on malaria-related death (Duggan *et al.* 2012). All studies are limited by the fact that it is impossible to isolate the effect of folic acid from that of other micronutrients.

There is also only limited trial evidence on the effect of the home fortification of complementary foods on malaria-related endpoints (Dewey & Baldiviez 2012). In a trial from South Africa, conducted among children aged 6–12 months of age, crushable tablets containing 88 µg of folic acid, 10 mg iron, and 12 other micronutrients were provided on a daily or weekly basis for mixing with porridge and did not have an effect on the incidence of fever over the 6-month study period (Smuts *et al.* 2005) (Table 3). In the trial from Ghana, children aged 6 months were assigned to three regimens providing a range of micronutrients (Adu-Afarwuah *et al.* 2007). These were crushable micronutrient tablets, small-quantity lipid based nutritional supplement (each including 9 mg iron and 80 µg folic acid alongside other micronutrients), or a micronutrient powder including 12.5 mg iron and 150 µg folic acid. At the end of the 6-month follow-up period, there were no differences in longitudinal fever prevalence between intervention groups. Furthermore, there were no differences in the prevalence of slide-positive malaria at end of follow-up between the three intervention groups, or between the intervention groups and a non-intervention control group (Adu-Afarwuah *et al.* 2008). A cluster-randomised trial in children aged 6–35 months in Western Kenya evaluated the community-based marketing and distribution of MNPs. At an average weekly intake per child of 0.9 sachets, the study did not find an effect on malaria prevalence (Suchdev *et al.* 2012). In subgroup analyses among the intervention villages, MNP use (as compared to MNP non-use) was not related to malaria parasitaemia or malaria-related hospitalisations or clinic visits (Suchdev *et al.* 2009).

Table 2. Preventive supplementation trials of folic acid and other micronutrients and malaria-related endpoints

Study, (Reference, Year)	Baseline age of study population	Daily trial regimen	Duration	Endpoint	Intervention group	Relative risk (95% CI)	Comment
Tanzania/ Main study, (Sazawal <i>et al.</i> 2006)	1–35 months:	Folic acid (50 µg) and iron (12.5 mg); folic acid, iron, and zinc (10 mg); or placebo. Children aged 1–11 months received half the dose.	Mean follow-up 383 days	Hospital admission or death	Folic Acid, Iron Folic Acid, Iron, Zinc Placebo	1.10 (0.99–1.22) 1.14 (1.03–1.27) 1.0 (REF)	Sulphadoxine-pyrimethamine standard of care but not administered as part of main study protocol. History of always sleeping under bed net 27%.
Tanzania/ Substudy, (Sazawal <i>et al.</i> 2006)	1–35 months	Folic acid (50 µg) and iron (12.5 mg); Folic acid, iron, and zinc (10 mg); or placebo. Children aged 1–11 months received half the dose.	Mean follow-up 342 days*	Malaria-related death or hospital admission Hospital admission or death	Folic Acid, Iron Folic Acid, Iron, Zinc Placebo	1.16 (1.00–1.34) 1.16 (1.01–1.34) 1.0 (REF)	Sulphadoxine-pyrimethamine used to treat clinical malaria at baseline and at scheduled visits at 6 and 12 months. History of always sleeping under bed net 38%.
Tanzania, (Veenemans <i>et al.</i> 2011)	6–60 months	Folic acid (93.75 µg), iron (18.5 mg), zinc (10 mg), and six other micronutrients; folic acid (93.75 µg), iron (18.5 mg), and six other micronutrients; or placebo.	Median follow-up: 331 days	Malaria incidence	Multi-nutrients (no zinc) Multi-nutrients + zinc Placebo	1.04 (0.87–1.23) 1.14 (0.96–1.35) 1.0 (REF)	Trial conducted among children with height-for-age z-score <−1.5. Effect estimates adjusted for potential confounders. Malaria cases treated at baseline and follow up with artemether-lumefantrine. Mosquito net use 30–36% in intervention groups.
Tanzania, (Duggan <i>et al.</i> 2012)	6 weeks	Folic acid (130 µg; 260 µg starting at age 7 months) and seven other vitamins, or placebo.	Median follow-up 681 days	Malaria-related death	Multi-nutrients Placebo	0.99 (0.89–1.10) 1.0 (REF)	Trial conducted among HIV-exposed children (11% HIV-infected at baseline). Sulphadoxine-pyrimethamine standard of care. No mosquito net use reported.

* Authors own calculation.

Table 3. Preventive home fortification trials of folic acid and other micronutrients and malaria-related endpoints

Study, (Reference, Year)	Baseline age of study population	Trial regimen	Duration	Endpoint	Intervention group	Percent	Comment
South Africa, (Smuts <i>et al.</i> 2005)	6–12 months:	Daily foodlet with 88 µg of folic acid, 10 mg iron plus 12 other micronutrients; weekly foodlet with 176 µg folic acid, 20 mg iron plus 12 other micronutrients; daily 10 mg iron foodlet; or placebo.	Planned follow-up 6 months	Prevalence of fever on the day of contact	Daily multi-nutrient Weekly multi-nutrient Daily iron Placebo	10.6 12.2 10.1 13.3	$P > 0.05$ for across-group comparisons. No information on malaria treatment or bed net use available.
Ghana, (Adu-Afarwah, 2007, 2008)	6 months	Daily micronutrient powder (150 µg folic acid, 12.5 mg iron plus four other micronutrients), crushable Nutri-tabs (80 µg folic acid, 9 mg iron, plus 14 other micronutrients), lipid-based spread (108 kcal, 80 µg folic acid, 9 mg iron, plus 17 other micronutrients); or no intervention.	Planned follow-up 6 months	Prevalence of fever on the day of contact Positive malaria smear at 12 months	Micronutrient powder Nutri-tabs Lipid-based spread Micronutrient powder Nutri-tabs Lipid-based spread Non-intervention	3.3 5.3 3.3 2.0 7.8 4.1 8.3	$P = 0.43$ for across-group comparisons. No information on malaria treatment or bed net use available. $P = 0.16$ for across-group comparisons.
Kenya, (Suchdev 2009, 2012)	6–35 months	Marketing of micronutrient powder containing (150 µg folic acid, 12.5 mg iron and 12 other micronutrients) vs. control.	12 months*	Prevalence of malaria parasitaemia Malaria clinic visit or hospitalisation	Intervention village Control village Powder use ‡ Powder non-use ‡	No effect † 1.00 (REF) 0.99 (0.91–1.07) § 1.00 (REF) §	Average weekly powder use 0.7–0.9 sachets. Insecticide-treated bed net use 83%.

*The cross-sectional evaluation at village level was conducted 12 months after start of the programme.

†No further details available.

‡Assessed within intervention villages only.

§Relative Risk.

There are multiple limitations of these home fortification trials in the current context. Given that folic acid was delivered alongside other micronutrients, it is impossible to isolate single-nutrient effects. The trials were not designed and powered to detect small increases in malarial morbidity. As recently described, the limited duration and, in the case of the study from Kenya the low dosages of home fortificants consumed, make generalisations impossible for programmes where home fortificants are used for longer durations and with higher frequency (Dewey & Baldiviez 2012).

Therapeutic trials

In trials conducted among children with malaria, supraphysiological dosages of folic acid were used to address the concern of depleted folate stores and increases in folate requirements owing to malarial haemolysis (Menendez *et al.* 2000). In a study from Gambia among children with uncomplicated *P. falciparum* malaria receiving SP, 10 mg folic acid (representing 113 times the RNI), or 5 mg for children <15 kg, led to a higher treatment failure rate as compared to placebo (van Hensbroek *et al.* 1995) (Table 4). In a study among Kenyan adults and children with anaemia and uncomplicated *P. falciparum* malaria receiving SP and iron, adjuvant supplemental folic acid (2.5 mg of folic acid d⁻¹ if <2 years of age and 5 mg a day if ≥2 years of age) had no effect on clinical failure, but increased parasitologic failure (Carter *et al.* 2005). In a trial among Zambian children with *P. falciparum* malaria and anaemia, a 2-week treatment with folic acid (1 mg d⁻¹) increased parasitaemia among children treated with the antifolate antimalarial drug SP but not in the group receiving the antifolate drug proguanil alongside atovaquone (Mulenga *et al.* 2006). These studies raise concerns that supraphysiological dosages of folic acid may inhibit SP drug activity.

Conclusion

Currently available data indicate that biochemical folate deficiency may be uncommon among pre-schoolers in sub-Saharan Africa. However, more

population-based assessments are needed from different sub-Saharan countries and that use recommended cut-off levels to denote biochemical folate deficiency. Specifically, such assessments should attempt to collect subnational data to identify groups at highest risk for deficiencies.

There is some limited evidence that high host folate status may favour growth of *P. falciparum* (Oppenheimer & Cashin 1986). Furthermore, in areas with high malaria endemicity, supraphysiological dosages of folic acid appear to be contraindicated as they may inhibit *P. falciparum* clearance with antifolate drugs (Carter *et al.* 2005; Mulenga *et al.* 2006; van Hensbroek *et al.* 2011). The potential harms or benefits related to the use of folic acid at RNI levels are less clear. Some *in vitro* evidence indicates that folic acid impairs the action of sulphadoxine against *P. falciparum* even at physiologic levels (Watkins *et al.* 1985) (Chulay *et al.* 1984) and this raises concerns regarding the use of folic acid in home fortification programmes in settings where antifolate antimalarial drugs remain in use. These concerns may grow once the WHO recommendations to use SP for IPTi (WHO 2010) and in SMC (WHO 2012) are implemented more widely in sub-Saharan Africa.

There are programmatic options to offset potential adverse effects related to folic acid contained in MNPs, as previously reviewed in the case of iron (Stoltzfus 2012). These options include strengthening ACT protocols and therefore limiting the use of SP for the treatment of malaria in areas with high resistance, as well as improving preventive malaria actions such as expanding the use of long-lasting insecticide bed nets. However, despite good progress, malaria is likely to remain an important problem and barriers to the use of ACT may remain. The use of MNPs could be limited to seasons where malaria-risk is reduced or their use could be discontinued during the use of SP in IPTi or SMC. However, these options are not satisfactory given that they would deprive children of other nutrients during crucial phases of their development. Screening for folate status is also unlikely to be a viable option in the near future.

Even though the folic acid contained in MNPs may benefit pre-schoolers who do not meet their recommended folate intake levels, these potential benefits

Table 4. Therapeutic folic acid supplementation trials during malaria infection

Study, (Reference, Year)	Eligibility criteria	Intervention arms	Duration	Endpoint	Intervention group	Failure (%)	Comment
The Gambia, (van Hensbroek <i>et al.</i> 1995)	Patients aged 6 months–9 years with clinical, uncomplicated malaria and confirmed <i>P. falciparum</i> parasitaemia	2 × 3 factorial design with Chloroquine [25 mg kg ⁻¹ (initial dose 10 mg kg ⁻¹ then 5 mg kg ⁻¹ every 12 h)] or sulphadoxine-pyrimethamine (25 mg kg ⁻¹ sulphadoxine and 1.25 mg kg ⁻¹ pyrimethamine); and • folic acid (5 mg for children <15 kg, 7.5 mg for children 15–20 kg, and 10 mg for children >20 kg), or • iron (82.5 mg d ⁻¹ elemental iron for children <20 kg, and 123.75 mg d ⁻¹), or • placebo	28 days (for 7 days initially; on day 7 an additional 21-day supply was given).	Parasitological failure at day 7 or 28	Chloroquine • Folic acid • Iron Sulphadoxine-pyrimethamine • Folic acid • Iron • Placebo	48.7 44.2 63.1	Failure rate for iron significantly lower than for placebo ($P = 0.02$).
Kenya, (Carter <i>et al.</i> 2005)	Patients of all ages with haemoglobin <11 g/dL and >5 g d ⁻¹ , clinical uncomplicated malaria, and confirmed <i>P. falciparum</i> parasitaemia	Randomized trial of folic acid (2.5 mg of folic acid d ⁻¹ for 30 days if <2 year and 5 mg d ⁻¹ if ≥2 year) or placebo. All participants received single dose of sulphadoxine-pyrimethamine by weight [0.5 tablet (12.5 mg of pyrimethamine and 250 mg of sulphadoxine) for 5–9.9 kg; subsequent 0.5 tablet increases per 10 kg interval up to 70 kg], and elemental iron for 30 days [0.5 tablet (30 mg elemental iron) for 5–9.9 kg; 0.5 tablet twice daily for 10–19.9 kg; 1 tablet twice daily for 20–39.9 kg; 1 tablet 3 times daily for ≥40 kg].	30 days	Parasitological failure over 28 days Clinical failure over 28 days	Folic acid Control Folic acid Control	No effect estimates reported No effect estimates reported	Failure rate for folic acid significantly higher than for control ($P < 0.0001$) No differences in failure rate between folic acid and control groups ($P = 0.70$)
Zambia, (Mulenga <i>et al.</i> 2006)	Patients aged 6–119 months with packed cell volume 15–21%, clinical uncomplicated malaria, and confirmed <i>P. falciparum</i> parasitaemia	2 × 2 factorial design with 17 mg atovaquone/7 mg proguanil kg ⁻¹ orally once daily for 3 days or single dose of sulphadoxine-pyrimethamine by weight (25 mg kg ⁻¹ sulphadoxine and 1.25 mg kg ⁻¹ pyrimethamine); and • folic acid (1-mg d ⁻¹ for 14 days); or • placebo	28 days	Parasitological failure in sulphadoxine-pyrimethamine group* Day 3 Day 7 Day 14 Day 28	Folic acid Control Folic acid Control Folic acid Control Folic acid Control	25% 2% 7% 2% 13% 3% 20% 30%	Folic acid significantly decreased parasite clearance at day 3 ($P = 0.003$). There were no significant differences ($P > 0.05$) at other time points.

*In atovaquone/proguanil group, folic acid had no impact on parasite clearance (data not shown in manuscript).

have to be balanced against potential risks related to the use of folic acid in malaria-endemic regions. These risks include increased malarial morbidity and lowered effectiveness of antifolate antimalarial medications. Such safety concerns have also been voiced by other researchers (Metz 1970; English & Snow 2006; Shankar 2008; Smith *et al.* 2008).

Therefore, as MNP programmes are growing in malaria-endemic regions in sub-Saharan Africa (UNICEF & CDC 2013), there is a need to determine whether folic acid can be safely used in these programmes. In parallel, updated global guidance is needed to direct MNP programmes.

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